Journal of Cardiology 67 (2016) 51–56

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Type 2 myocardial infarction: A descriptive analysis and comparison with type 1 myocardial infarction

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ARTICLE INFO

Article history:
Received 1 February 2015
Received in revised form 14 March 2015
Accepted 7 April 2015
Available online 5 May 2015

Keywords:
Type 2 myocardial infarction
Triggers
Plaque rupture
Mortality
Major adverse cardiovascular events

ABSTRACT

Background: While 'plaque rupture' is the paradigm of type 1 myocardial infarction (T1MI), T2MI is myocardial necrosis secondary to oxygen supply-demand mismatch. Being a heterogeneous and rather newly defined group, data are lacking about T2MI.

Methods: A retrospective review of medical records of patients diagnosed with T2MI in the Rabin Cardiology Center, Israel between the years 2007 and 2012 was performed. Following a descriptive analysis, we used multivariate time dependent models to estimate the association of T2MI with the risk for 30-day, 1-year, and 5-year all-cause-mortality and major adverse cardiovascular events (MACE), and compared it to a T1MI group matched for age, gender and electrocardiographic changes.

Results: The study included 107 T2MI (and 107 T1MI) patients. Sepsis, anemia, and atrial fibrillation were the most common etiologies. Triple anti-thrombotic therapy was given to 22% of T2MI patients (vs. 82% of T1MI patients, $p < 0.001$). Twenty-five percent were managed using urgent percutaneous coronary intervention. Angiography unmasked acute plaque rupture in 29% of T2MI patients group. Compared to T1MI, T2MI was associated with higher all-cause-mortality rate: adjusted-hazard-ratio 7.14 (1.31–38.9) at 30 days, 3.42 (1.51–7.75) at 1 year, and 2.08 (1.14–3.81) at 5 years follow-up. MACE risk was consistent between T2 and T1MI patients.

Conclusions: The most common T2MI triggers are sepsis, anemia, and atrial fibrillation. Compared to a T1MI population, T2MI is associated with higher short- and long-term mortality rates but equal cardiovascular mortality and MACE risk. As many as 30% may harbor plaque rupture and in fact have T1MI.

Introduction

Type 2 myocardial infarction (T2MI) is defined as cardiomyocyte necrosis caused by conditions other than atherosclerotic coronary artery disease (CAD) and secondary to decrease in oxygen supply (e.g. hypoxemia, anemia, hypotension, and endothelial dysfunction) and/or increased demand (e.g. tachycardia, arrhythmia, and sepsis) [1]. Although believed to constitute as many as 25% of all MIs in hospitalized patients [2] and strongly associated with a high mortality rate [3,4], as a heterogeneous and relatively newly defined group, little is known about T2MI patients. Since 2007, when the diagnosis was first introduced by the Universal definition, it raised awareness, documentation and quality review programs, and holds promise to improve outcome for these patients in the future [5]. While plaque rupture is the designation paradigm of T1MI, it is often difficult to exclude atheroembolic acute coronary events in patients thought to suffer T2MI. Whether and when to attempt revascularization among patients hospitalized with severe sepsis and ischemic electrocardiographic (ECG) changes with new elevated troponin level is based on clinical judgment. The magnitude of benefit, if any, of anti-platelets and anti-coagulant medications in these patients has yet to be defined. Apart from treating the underlying condition, there are neither guidelines nor a consensus on the optimal management of T2MI

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http://dx.doi.org/10.1016/j.jjcc.2015.04.001
0914-5087/

patients [6]. Better characterization of T2MI patients may help to predict which patients suffer pure secondary MI and which harbor acute coronary events. The objective of our study was to characterize T2MI patients concerning baseline characteristics, clinical presentation, management, and outcome, with a comparison to a T1MI patient group matched for age (±2 years), sex, and ST-elevation (STE).

Methods

In our cardiology department at Rabin Medical Center in Israel, we used electronic medical, pharmacy, and laboratory record systems to review records of patients admitted and diagnosed with T2MI between the years 2007 and 2012. We validated the diagnosis and included only patients who fulfilled both of the following criteria:

1. Detection of a rise and/or fall of cardiac troponin T (cTnT) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
   A. Symptoms of ischemia.
   B. New or presumed new significant ST–T changes, left bundle branch block (LBBB), or pathologic Q waves.
   C. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality (RWMA).

   cTnT assay was performed on Roche Elecsys 2010 (Basel, Switzerland) and Roche Cobas e 411 instruments, using the electrochemiluminescence immunoassay. Between 2007 and 2010 we used cTnT 4th Gen. The limit of quantification (functional sensitivity) was 30 ng/L, and the URL (99th percentile) was 10 ng/L. From 2010 until the end of the study we used cTnT hs (high sensitive). The limit of quantification (functional sensitivity) was 13 ng/L, and the URL (99th percentile) was 14 ng/L.
2. At least one of the following conditions considered to trigger imbalance between myocardial O_2 supply-demand (supported, partially, on data from the literature [2,5,7–9]):
   A. Sepsis-systemic inflammatory response syndrome (SIRS) which consists of ≥two of the following: fever > 38 °C, tachypnea > 24 breaths/min, tachycardia > 100 beats/min, leukocytes > 12 K/μL, in the context of clinically suspected/documented infection.
   B. Shock – defined as systolic blood pressure (BP) < 90 mmHg and/or diastolic BP < 60 mmHg together with evidence of systemic hypo-perfusion (lactatemia).
   C. Anemia (severe) – defined as a fall in ≥2 g/dL hemoglobin (Hb) and/or Hb < 10 g/dL and/or a need to use blood products.
   D. Active bleeding – visualization of blood in stool, vomit, gastric aspirate, or endoscopy.
   E. Tachyarrhythmia – ventricular rate > 120/min excluding sinus tachycardia.
   F. Bradyarrhythmia – requirement of medical treatment or cardiac pacing.
   G. Respiratory failure – requirement of mechanical ventilation (invasive or non-invasive).
   H. Hypertensive crisis – systolic BP > 180 mmHg and concomitant progressive retinopathy and/or encephalopathy.

We then used a matching algorithm which sequentially searched a 4524 T1MI patient cohort (all T1MI patients admitted to our department between years 2007 and 2012), matching for sex, ST segment elevation, and searching for the closest match for age (year ±2). Each selected pair was then removed from the search algorithm until a 1:1 matching process was completed. T1MI diagnosis was validated according to the first of the two above-mentioned criteria.

The study protocol was approved by the Helsinki Committee of the Rabin Medical Center.

Definition of covariates:

After descriptive analysis of baseline characteristics and clinical presentation, we used multivariate time dependent Cox regression models to estimate the association of T2MI with the risk for 30-day, 1-year, and 5-year major adverse cardiovascular events (MACE) [cardiovascular (CV)-death, urgent percutaneous coronary intervention (PCI), stroke, and re-MI] and all-cause-mortality. CV mortality was defined as death due to acute coronary and/or aortic syndrome, cardiac arrhythmias, congestive heart failure (CHF), stroke, pulmonary emboli, or during cardiac interventions. All other deaths were considered non-CV. The cause of death was adjudicated blindly with respect to MI type. Re-MI was defined as recurrence of chest pain or ECG changes and new cTnT elevation. Urgent PCI was defined as PCI for re-MI or unstable angina during follow-up. CHF was defined as left ventricular ejection fraction (LVEF) < 40% and/or a history of CHF. Patients without history of CHF but with missing LVEF data were excluded from the CHF analysis. ECG changes were considered ischemic when there was evidence of new ST segment deviation, T wave inversion, LBBB, or pathologic Q wave. We conducted angiographic characterization of coronary lesions morphology using features of complexity previously described by Ambrose et al. [10–13]. Lesions were considered 'complex' if they exhibited either: (A) An intraluminal filling defect consistent with thrombus, defined as abrupt vessel cutoff with persistence of contrast or filling defect observed in multiple views; (B) Plaque ulceration, defined by the presence of contrast beyond, but contiguous to the vessel lumen; or (C) Two or more of the following: (a) fissuring, defined by intra-plaque dye penetration not meeting definition of ulceration; (b) plaque irregularity, defined by irregular margins or overhanging edges; or (c) intraluminal haziness. Lesions not meeting these criteria were considered to be 'noncomplex.' The angiographic analysis and interpretation were carried out by an experienced cardiologist blinded to the original angiographic interpretations and to the MI type as well as to the clinical outcome. We only analyzed lesions that were associated with at least 50% stenosis.

Statistical methods

Categorical data were reported as numbers (percentages), and continuous data were reported as means [±standard deviations (SD)] and medians [±interquartile ranges (IQRs)]. Comparisons between groups for categorical data were made with the Chi-square or Fisher's exact tests, whereas continuous data were compared using two-sample *t*-tests or Mann–Whitney test. Univariate Cox proportional hazards models were used to assess the impact of MI type and other variables on all-cause-mortality, CV-mortality, and MACE. MI type and variables with $p < 0.2$ in the univariate analysis were included in the multivariate analysis. Cox proportional hazards models were used to assess the impact of MI type on all-cause-mortality, CV-mortality, and MACE, while controlling for confounders. As the groups were matched for age (±2 years), sex, and STE, the only other covariates included in the multivariate analysis, specifically: ischemic heart disease (IHD), diabetes mellitus, chronic kidney injury (CKI), LVEF at presentation, pulmonary congestion, Hb level (g/dL), creatinine (Cr) level (mg/dL), and cTnT level (ng/mL). Analyses were repeated separately in patients with or without sepsis, with or without anemia, and with or without arrhythmia. These stratified analyses allowed us to explore the associations between T2MI and the primary outcomes differences according to T2MI major subgroups. Kaplan–Meier curves were constructed to estimate the survival function of all-cause-mortality, CV-mortality, and MACE within T2MI

and T1MI groups. Patients were censored at MACE, CV-mortality, all-cause-mortality, and end of follow-up after index MI, whichever came first. For all data analyses we used IBM-SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA) and R version 3.0.2. All *p*-values were two-sided, and a *p*-value of <0.05 was considered statistically significant.

Results

Between the years 2007 and 2012 there were 4283 patients admitted with MI to our Cardiology Department. Among those, we identified 148 patients admitted with T2MI after review of medical records, 41 patients were excluded from the study: 15 had insufficient data on serum cTnT level (rise and/or fall were not demonstrated), 12 had no trigger as defined by the inclusion criteria, 8 had features of takotsubo cardiomyopathy, 2 were diagnosed with aortic dissection, 2 had type 4a (periprocedural) MI and 2 4b (stent thrombosis) MI. Therefore, the final analysis included 107 verified T2MI and 107 properly matched T1MI patients. Patients' baseline characteristics and clinical presentation (including the matched parameters) are summarized in Table 1.

The mean age of T2MI cohort was 74 years, with 35% female patients. About half of the patient cohort had diabetes mellitus, 54 patients (72% of patients with available pre-MI echo data) had good baseline LV function. STEMI on admission was detected in 11 (10.3%) patients, and ischemic ECG changes were absent in 25 (33.1%) patients. While chest pain/discomfort was significantly less frequent among T2MI patients compared to T1MI patients (61.3% vs. 96.3%, $p < 0.001$), pulmonary congestion was significantly more prevalent (34.6% vs. 16.8%, $p = 0.003$). There was no difference between the cohorts in terms of LV function or RWMA.

Compared with T1MI patients, T2MI mean serum creatinine level was higher (1.6 mg/dL vs. 1.0 mg/dL, $p < 0.001$), and mean serum Hb was lower (10.2 g/dL vs. 13.3 g/dL, $p < 0.001$). The mean serum cTnT level was 1.0 (±1.4) ng/dL and 1.4 (±2.3) ng/dL in T2 and T1 patients, respectively. This difference did not reach a statistically significant threshold (Table 1).

A quarter of the cases developed post-surgically, the majority following vascular surgery. The mean surgery-to-MI time was 2.1 days (±2.3 SD). As sepsis was the most prevalent trigger, fever was present in 36.4%, and positive blood cultures were obtained in 5.6%. More than a third of the patients had an arrhythmic trigger – all were tachyarrhythmia, most commonly rapid atrial fibrillation (AF). In the majority of patients, more than one trigger was present.

The majority of T2 patients were treated with aspirin, less than half were treated with dual anti-platelet therapy, and only 38% were treated with an anti-coagulant. Triple anti-thrombotic therapy (aspirin plus anti-coagulant plus ADP-antagonist medication) was given to 22% and 82% of T2 and T1 patients, respectively ($p < 0.001$). Excluding statins, all other drugs commonly used for the intensive medical management of acute coronary syndrome were used significantly less in T2 patients. Repeating data analysis after excluding patients with anemia or active bleeding did not change these differences in the medical management strategy. Only 29 (27.1%) patients had been managed invasively with urgent coronary angiography. Of those, less than half (48.4%) underwent mechanical coronary reperfusion (compared with 79.1% of T1MI patients). Of note, 30.8% of T2MI patients suitable for coronary reperfusion were transferred to coronary artery bypass graft surgery as compared with 7.3% in the T1 group. Angiographic analysis of the study group revealed acute plaque rupture characteristics in 29% of the coronary lesions (Fig. 1).

Finally, with multivariate analysis, we estimated the association between MI types and the risk for 30-day, 1-year, and 5-year MACE and all-cause-mortality. At all time intervals, T2MI was associated with a significant increase in all-cause-mortality. By contrast, MACE risk was consistent between T2MI and T1MI patients. Results are summarized in Table 2. The Kaplan–Meier curves for all-cause-mortality and MACE for T2MI vs. T1MI matched patients are shown in Fig. 2.

The 11 patients who presented with STE-T2MI did not show any difference in clinical characteristics compare with the other 96 T2MI patients. This is probably because the study is underpowered to answer this question reliably. Moreover, only three STE-T2MI patients had plaque rupture features on coronary angiography, which is the same frequency observed in NSTE-T2MI.

We also compared, using multivariate subgroups analysis, outcomes for the invasive (urgent PCI, 29 patients) vs. conservative (no PCI, 78 patients) T2MI patients management: the adjusted-hazard-ratio (HR) and 95% confidence-interval (CI) for all-cause-mortality was 0.57 (0.16–1.99) at 30 days ($p = 0.378$) and 0.59 (0.26–1.35) at 1 year ($p = 0.208$). The adjusted HR for MACE was 1.18 (0.36–3.83) at 30 days ($p = 0.784$) and 0.61 (0.23–1.62) at 1 year ($p = 0.318$).

Table 1
Baseline characteristic and clinical presentation, *n* (%).

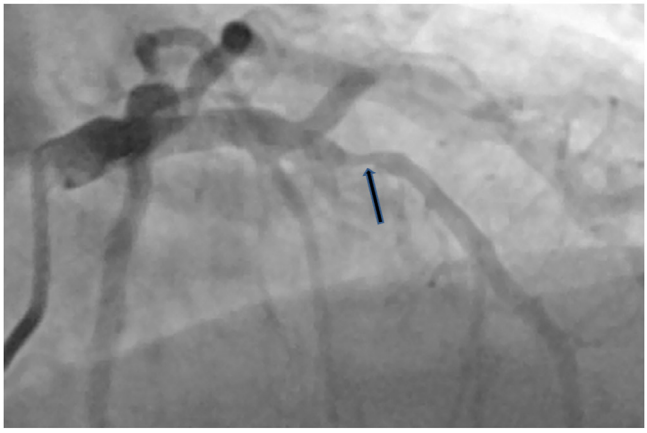
	Type I MI	Type II MI	*p*-Value
Baseline characteristic			
Age (years)	72 (±12.5)	74 (±10.4)	0.134
Female	38 (35.5)	38 (35.5)	1
Diabetes mellitus	54 (50.5)	54 (50.5)	1
Baseline LV function (%)			0.8555
Good LV function	37 (68.5)	54 (72)	
Mild LVD	6 (11.1)	6 (8)	
Moderate LVD	6 (11.1)	10 (13.3)	
Severe LVD	5 (9.3)	5 (6.7)	
Ischemic heart disease	50 (46.7)	68 (63.6)	0.013
Past angioplasty	38 (35.8)	49 (46.2)	0.125
Hypertension	82 (76.6)	87 (81.3)	0.402
Hypercholesterolemia	69 (64.5)	82 (76.6)	0.051
Chronic kidney injury	17 (15.9)	29 (27.1)	**0.046**
Smoking	41 (38.3)	44 (41.9)	0.594
Dementia	4 (3.7)	4 (3.7)	1
Malignancy	4 (3.7)	4 (3.7)	1
Presentation			
ST segment elevation	11 (10.3)	11 (10.3)	1
In hospital	4 (3.7)	51 (47.7)	**<0.001**
ECG ischemic changes	75 (70.1)	71 (66.4)	0.557
Chest pain	103 (96.3)	65 (61.3)	**<0.001**
Dyspnea	38 (35.5)	78 (72.9)	**<0.001**
Pulmonary congestion	18 (16.8)	37 (34.6)	0.003
LV function at presentation			0.448
Good LV function	42 (40.8)	40 (40.4)	
Mild LVD	23 (22.3)	19 (19.2)	
Moderate LVD	28 (27.2)	23 (23.2)	
Severe LVD	10 (9.7)	17 (17.2)	
RWMA at presentation	80 (77.7)	74 (74)	0.541
Troponin T [ng/mL]	1.4 (±2.3)	1 (±1.4)	0.128
Creatine kinase [U/L]	584.9 (±858.1)	602.6 (±242.5)	0.944
Creatinine [mg/dL]	1 (±0.4)	1.6 (±1.5)	**<0.001**
Hemoglobin [g/dL]	13.3 (±2.1)	10.2 (±2.2)	**<0.001**

Categorical data reported as number and percentage (%). Continuous data reported as means (±standard deviations). MI, myocardical infarction; LV, left ventricle; LVD, LV dysfunction; RWMA, regional wall motion abnormality. Significance of bold values is $p < 0.05$.

Discussion

It is a clinical challenge to determine whether myocardial necrosis is secondary to supply-demand oxygen mismatch [14]. Troponin is a sub-optimal prognostic marker in critically ill patients [15–17], and sepsis, pulmonary disease, renal failure, and stroke may cause elevated cTn levels [18–21], reflecting non-ischemic cTn elevation. Therefore, it is essential to distinguish between the ischemic nature of myocardial injury by clinical signs

a : Coronary angiography of T2MI patient with 75% mid LAD stenosis.
The patient presented with NSTEMI while being admitted with pneumonia.



b : Coronary angiography of T2MI patient with 95% 'plaque rupture' in the proximal dominant RCA.
The patient presented with NSTEMI while being admitted with gastrointestinal bleeding.

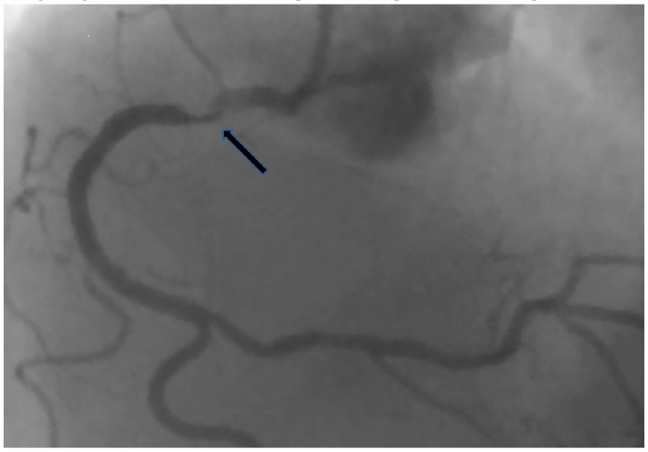


Fig. 1. Examples from coronary angiography of two type 2 myocardial infarction study patients showing "non-complex" (a) and "plaque rupture" lesions characteristics (b).

and symptoms, ECG changes and cardiac imaging [1], and then to distinguish the cause (T1MI vs. T2MI). We restricted our study to patients with anginal symptoms, ischemic ECG changes, or RWMA, to include only patients with ischemic nature troponin dynamics. Furthermore, as there are no internationally accepted criteria, we had meticulously pre-defined our T2 trigger standards, based, to some extent, on data from the literature. Consequently, we describe herein 107 T2MI and 107 T1MI patients admitted to our center during a 6-year period. The groups were matched according to three key baseline characteristics to empower significance to MI type, rather than to the effect of the aforementioned important variables. During the 6-year study period, T2MI was diagnosed in 2.2% of MI patients admitted to our center. In line with our results, Morrow et al. and Bonaca et al. classified T2MI in 3.5% of MI patients [22], Melberg et al. and Szymański et al. in 1.6% and 2%, respectively [23,24]. Conversely, Javed et al. reported T2MI in 29.6% of MI patients [25], and Saaby et al. in 26% [2]. There are only few studies on T2MI, and inclusion criteria between studies vary. The lack of consistency in patients' selection criteria is the likely cause for this heterogeneity in incidence. STE-T2MI is reported to represent 0–23% of T2MI in different studies [2–4]. In our study, 10% of T2MI patients were presented with STE. While the mean cTnT level was lower in T2MI compared with T1MI patients, possibly since the study was underpowered, this difference did not reach the statistically significant threshold, as it did in other studies [2]. An intriguing finding was that while both groups presented with similar LV function level, dyspnea and pulmonary congestion were significantly more frequent in T2 patients. This may be explained by a non-cardiogenic component in the T2MI pulmonary congestion, as SIRS is more frequently present in these patients. Apart from our study, only one study, to the best of our knowledge [2], predefined criteria for triggers to reflect myocardial O_2 imbalance. As opposed to our study, septic patients were excluded from the study, reasoning that cTnT elevation in sepsis does not reflect overt myocardial ischemia. Despite the evidence that myocardial necrosis in septic patients may reflect a non-ischemic inflammatory reaction of the myocardium, as was shown in some cardiac magnetic resonance imaging studies [21], we argue that in the presence, and only in the presence of ischemic clinical scenario (chest pain, ischemic ECG changes, or cardiac imaging), referring troponin dynamics as "non-ischemic" is both impractical and inappropriate. Moreover, as SIRS can cause tachycardia (as tachycardia is one of the SIRS criteria), it may elevate myocardial oxygen demand and cause demand-supply imbalance. Also in SIRS, endothelial cells are precociously exposed to signaling molecules and physical stresses which lead to increase in inducible nitric oxide synthase expression and a negative feedback on endothelial nitric oxide synthase expression, with subsequent deregulation of nitric oxide signaling. Endothelial dysfunction is known to play a major role in the pathophysiology of organ dysfunction in sepsis [26]. We maintain sepsis to be the most common T2MI etiology.

There are neither guidelines nor consensus for managing T2MI patients [1,8,9]. Yet these patients are frequently treated with antithrombotic medications and or PCI, based solely on empirical decision making [27]. To date, there has been no study conducted to seek and verify the effectiveness of these treatments in T2MI. As it is apparently caused by a non-thrombotic mechanism, it is intuitive that such approaches will not be as effective as in T1MI. Indeed, such treatments are contraindicated in many T2 patients due to high risk for bleeding. We found that, even after excluding anemic and bleeding patients, triple-antithrombotic therapy was given to only 22% of T2MI patients, and that only 29 (27.1%) of T2MI patients had been managed with urgent coronary angiography. PCI was not associated with improved outcomes, albeit our study is underpowered to address this question reliably. A significant CAD was demonstrated in 75% of T2MI patients as opposed to 55% reported in the literature [2]. As we analyzed lesion morphology, we diagnosed acute plaque rupture in 29% of the patients. Recently, Hanson et al. [10] described the angiographic features of perioperative MI following non-cardiac surgery: 59% had plaque rupture features and 41% had stable coronary features.

It is reasonable to assume that in specific T2MI patients, the element of inflammation and hyper-coagulation cause acute progression of pre-existing coronary lesions (T1MI), on top of

Table 2
Risk for all-cause-mortality and MACE, T2MI vs. matched T1MI.

Outcome	HR_{Adj}[a]	(95% CI)	*p*-Value
All-cause-mortality			
30 days	7.14	(1.31–38.9)	**0.023**
1 year	3.42	(1.51–7.75)	**0.003**
5 years	2.08	(1.14–3.81)	**0.017**
MACE			
30 days	1.07	(0.49–2.31)	0.871
1 year	1.05	(0.51–2.17)	0.895
5 years	1.02	(0.59–1.76)	0.950

MACE, major adverse cardiovascular events; T2MI, type 2 myocardial infarction; T1MI, type 1 myocardial infarction; HR_{Adj}, adjusted-hazard-ratio; CI, confidence interval.
[a]Adjusted for: ischemic heart disease, chronic kidney injury, left-ventricular ejection fraction at presentation, pulmonary congestion, hemoglobin level, creatinine level [mg/dL] and cardiac troponin T level (ng/mL).
Significance of bold values is $p < 0.05$.

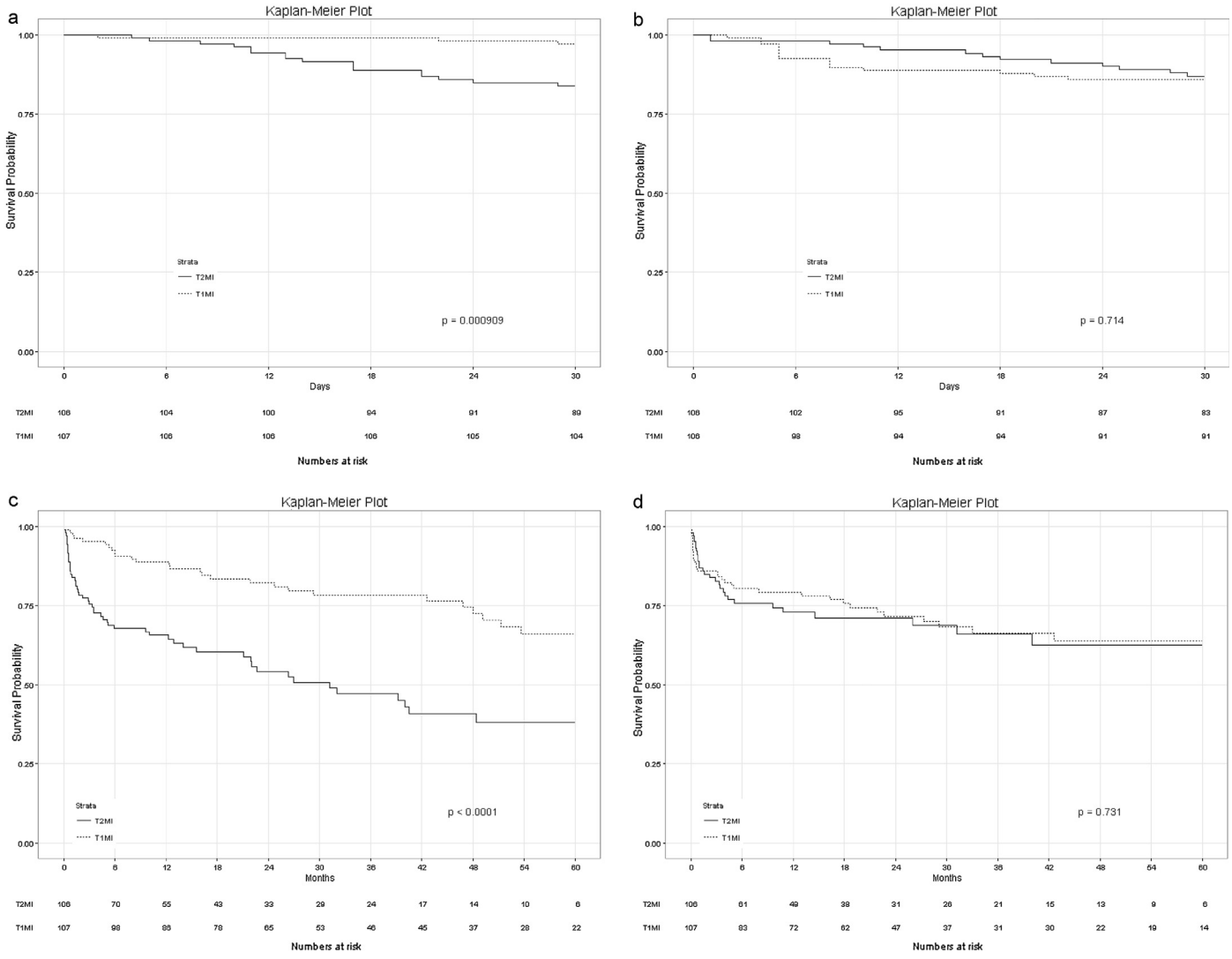


Fig. 2. (a) Kaplan–Meier curves for 30-day all-cause-mortality: T2MI vs. T1MI patients. (b) Kaplan–Meier curves for 30-day MACE: T2MI vs. T1MI patients. (c) Kaplan–Meier curves for 5-year all-cause-mortality: T2MI vs. T1MI patients. (d) Kaplan–Meier curves for 5-year MACE: T2MI vs. T1MI patients. T2MI, type 2 myocardial infarction; T1MI, type 1 myocardial infarction; MACE, major adverse cardiovascular events.

the oxygen mismatch myocardial damage (T2MI) [27]. Careful clinical judgment and identification of the more dominant ischemic mechanism are the key in determining a proper treatment strategy.

Compared with the T1MI patients group, we found T2MI to be associated with HR 7.14 ($p = 0.023$) for 30-day mortality, HR 3.42 ($p = 0.003$) for 1-year mortality, and HR 2.08 ($p = 0.017$) for 5-year mortality. The highest mortality risk appeared during the first 6 months after the index event, after which the slopes of the mortality curves almost paralleled (Fig. 2c). We found T2MI not to constitute higher risk for CV-death or MACE compared to T1MI. Similar findings were shown in a post hoc analysis of the TRITON-TIMI 38 Trial that reported increased but consistent CV-death across T1 and T2MI patients [3].

Limitations

Our study has the inherent limitations of a retrospective study. The association between T2MI and mortality may still be over-estimated due to unmeasured confounders, and our subgroup analyses are limited by small sample size. Specifically, few angiograms were done in the type 2 patients. Additionally, our study may suffer a selection bias, since it is based on records from cardiology department admissions, while at least half of T2MI patients are admitted to non-cardiology departments [2]. In cardiology wards, T2 patients may be younger and suffer less comorbidity than T2 patients admitted to other wards. Nonetheless, the mean age and other baseline characteristics of T2MI patients in our study are similar to those reported in other studies [2,4,20,22,25].

Summary and conclusions

T2MI is still an ambiguous diagnosis, most commonly caused by sepsis, arrhythmia, and anemia. It is associated with higher mortality and equal CV-mortality and MACE compared to T1MI. While it is a clinical diagnosis, as many as one third of the T2MI patients have in fact angiographic diagnosis of T1MI, with plaque rupture characteristics. Larger prospective studies are warranted, with an adaption of universal consensus criteria.

Funding

None of the authors have any grants, contracts, or other forms of financial support to declare of or relationship with industry and financial associations.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgments

All the authors have participated in the conceptual formulation of the study and data collection. Dr. Landes, Dr. Bental, Dr. Orvin, and Prof. Kornowski performed the data analysis and manuscript preparation. The authors also warrant that the article is original and none of the paper's content has been previously published.

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